REMARKS

Claims 1-74 are pending in the above-referenced application. The Examiner has rejected claims 1-45. Claims 46-74 are withdrawn from consideration and have been canceled herewith. Claims 1-3 and 30-32 have been amended. New claim 75 has been added, and support for claim 75 reciting RNA inhibiting agents can be found on page 3, line 8. Applicant respectfully submits that no new matter is presented with these amendments. Applicant reserves the right to prosecute without prejudice in a future application subject matter amended from the claims by the Amendment submitted herewith. Applicant respectfully requests consideration of the amended claims presented herein and respectfully submits that claims 1-45 and 75 are now in condition for allowance.

Applicant has amended the Specification as requested by the Examiner to delete embedded hyperlinks and to add SEQ ID NOs. A proper sequence listing including a computer readable form and a paper copy are also submitted herewith.

I. Rejection of claims 1, 2, 3, 30-32, 36-42, and 45 under 35 U.S.C. § 102(b):

The Examiner has rejected claims 1, 2, 3, 30-32, 36-42, and 45 under 35 U.S.C. § 102(b), as being anticipated by Nakanishi *et al.* (*Proc. Natl. Acad. Sci. USA*, 92:4352-56, May 1995). Examiner states that Nakanishi *et al.* teach the expression of antisense p21 RNA in G_0 arrested cells which resulted in DNA synthesis and entry of the cells into mitosis. Nakanishi *et al.* however only teaches the expression of antisense p21 RNA and entry into the cell cycle in human fibroblasts. Nakanishi *et al.* does not teach the claimed invention which as amended herewith recites the use of either stem or progenitor cells. Since Nakanishi *et al.* does not teach this element of the claimed invention, Nakanishi *et al.* does not anticipate the claimed invention, and therefore, Applicant requests that the rejection be removed.

II. Rejection of claims 1, 2, 30-32, 36-42, and 45 under 35 U.S.C. § 102(b):

The Examiner has rejected claims 1, 2, 30-32, 36-42, and 45 under 35 U.S.C. § 102(b) as being anticipated by Waldman *et al.* (*Cancer Res.* 55:5187-90, 1995). Examiner states that Waldman *et al.* teach a method wherein clones comprising a homozygous deletion of p21 resulted in abrogation of the G_1 cell cycle checkpoint such that all cells passed through S phase

and resulted in the growth and proliferation of the cells. The disclosure of Waldman *et al.*, however, is limited to the human colorectal cancer cell line HCT-116. Since the present invention recites stem and progenitor cells, Waldman *et al.* cannot anticipate the claimed invention as amended herewith. In addition, the work performed by Waldman *et al.* in established cell lines, which have been selected to grow *in vitro*, is not indicative of the effect in primary stem or progenitor cells from patients. Applicant requests that the rejection be removed.

III. Rejection of claims 1-21, 27, and 30-45 under 35 U.S.C. § 103:

Claims 1-21, 27, and 30-45 stand rejected under 35 U.S.C. § 103, as being unpatentable over Nakanishi *et al.* as applied above, and further in view of Rivard *et al.* (*J. Biol. Chem.* 271(31):18337-18341, 1996). Examiner cites Rivard *et al.* as teaching that enforced expression of p27 in cells causes G_1 arrest and that reduced expression of p27 using antisense constructs results in DNA synthesis and the growth and proliferation of cells. Applicant submits that given the limited teachings of these references, even if they were combined, they do not render the claimed invention obvious.

First and foremost, neither of the references teaches the use of stem cells or progenitor cells as recited in the presently amended claims. As described above, Nakanishi *et al.* used human fibroblast cells (HCA2 cells) isolated from neonatal foreskins. Rivard *et al.* used Chinese hamster lung fibroblasts (CCL39). There is no teaching or even suggestion in either of the references that stem cells or progenitor cells might be used. Given the substantial differences in cell biology between fully differentiated fibroblasts and pluripotent stem and progenitor cells, there is no suggestion that stem or progenitor cells could be manipulated in the same way using p21 and/or p27 as described in the cited references. Furthermore, there is certainly no reasonable expectation that experiments performed in fully differentiated cells could be easily translated into stem and progenitor cells, whose cell cycle control can not reasonably be assumed to be the same as that found in fully differentiated cells. Therefore, the cited references even when combined fail to teach or suggest the use of stem and progenitor cells as claimed. Applicant therefore requests that the rejection be removed on this basis alone.

In addition with respect to claims 4-6 and 35, wherein both p21 and p27 are inhibited, there is no teaching or suggestion in the cited references to combine both teachings to achieve an

inhibition of both p21 and p27. In reading each reference, it seems that inhibiting p21 or p27 will allow the fibroblasts to exit G_0 and enter the cell cycle. Since at first glance both genes seem to have the same function, there would be no reason to inhibit both of these activities in any one cell. Therefore the cited references would seem to teach away from the claimed invention of claims 4-6 and 35. Applicant therefore requests the withdrawal of the rejection of those claims reciting the inhibition of both p21 and p27 activity.

IV. Rejection of claims 3-6 and 22-29 under 35 U.S.C. § 112, first paragraph:

Claims 3-6 and 22-29 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner maintains that since the Applicant does not describe the complete structure of the agents that are useful in inhibiting the activity of p21 and p27 in the claimed invention, "the specification does not describe the claimed agents in such full, clear, concise and exact terms so as to indicate that Applicant had possession of these molecules at the time of filing of the present application." Therefore, the Examiner believes the written description requirement has not been met. Applicant disagrees that the written description has not been met because one of ordinary skill in this art reading the Specification would understand that any agent, including small molecules, proteins, peptides, anti-sense molecules, *etc.*, that inhibit p21 or p27 activity would be useful in the present invention.

At the time of filing, the inventors recognized that p21 and p27 activities are critical in cell cycle control in stem and progenitor cells and that therefore the inhibition of either or both of these activities by any agent is useful in practicing the claimed invention of expanding cell populations. As evidence, the inventors provide in the Examples studies using anti-sense technology to inhibit p21 activity in order to expand cell populations. The inventors clearly had in mind, at the time of filing, any agent that inhibits p21 and p27 as useful in the present invention (see page 18, beginning at line 17). As evidence, listed in dependent claims 22-29 are various categories of agents that can be used to inhibit p21 or p27 activity. Clearly, the inventors understood that any and all agents that inhibit p21 or p27 are useful in the present invention. It would be unfair for the inventors to be limited to only the agents that they can specifically name.

Any new agents that were later discovered could then be used to practice the invention without infringing the Applicant's claims. Such a result would not support the policy considerations behind patent law, that is, to promote the arts by granting inventors exclusive rights commensurate in scope with their invention for a limited time. It would be understood by one of ordinary skill in this art that they could go to the literature to find agents that have been found to inhibit p21 or p27 activity, or using the information provided in the Specification, one could screen for agents able to inhibit p21 and p27. As but one example, in the Specification at page 44, Example 3 describes the use of p21 anti-sense technology to inhibit the activity of p21. Clearly one of skill in the art reading the Specification would understand that the inventors were in possession of the claimed invention at the time of filing. Applicant therefore requests that the rejection be removed.

V. Rejection of claims 1-45 under 35 U.S.C. § 112, second paragraph:

Claims 1-45 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and definitely claim the subject matter which applicant regards as the invention. Particularly, the Examiner has objected to the language, "less than wild-type p21 activity" and "less than wild-type p27 activity". The Examiner states that the term, wild type activity, is unclear since p21 and p27 activity may be different depending on the cell. Applicant disagrees. The wild type terminology used in the present claims would be clear and definite to one skill of ordinary skill in the art reading the application. Although the absolute level of p21 and p27 activity in a cell may vary, one of ordinary skill would understand that the inventor in the claimed invention is decreasing the amount of p21 and/or p27 activity compared to that which is normally found in the cell under the same conditions. Therefore, an untreated cell or a genetically unaltered cell would have "wild type" p21 and p27 activity. For example, with respect to claim 2 in which the p21 gene of the cell has been disrupted, the p21 activity is less than the p21 activity in the cell before the genetic lesion, that is the "wild type" activity. Applicant submits that the term "wild type activity" is clear to those of ordinary skill in the art, and therefore, Applicant requests that the rejection be removed.

If it is believed that a telephone conversation would expedite matters, the Examiner is invited to contact the undersigned at (617) 248-5215. Although it is believed that there is no fee associated with this amendment, if Applicant is mistaken, please charge any fees to our Deposit Account Number: 03-1721.

Respectfully Submitted,

C. Hunter Baker, M.D., Ph.D.
Registration Number: 46,533

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
Phone: (617) 248-5215
FAX: (617) 248-4000
Date: October 8, 2003

Certificate of Mailing

I certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

October 8, 2003
Date

Signature

Linda M. Amato
Typed or Printed Name of person signing certificate